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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/729,520	12/04/2000	Ana Rodriguez	GC647	4557

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GENENCOR INTERNATIONAL, INC.
ATTENTION: LEGAL DEPARTMENT
925 PAGE MILL ROAD
PALO ALTO, CA 94304

EXAMINER	
EPPERSON, JON D	
ART UNIT	**PAPER NUMBER**
1639	

DATE MAILED: 06/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/729,520	RODRIGUEZ ET AL.	
	Examiner	Art Unit	
	Jon D Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Request for Continued Examination (RCE)

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/9/04 has been entered. Claims 1-6 and 8 were pending. Applicants amended claim 1. No claims were added or canceled. Therefore, claims 1-6 and 8 are still pending. An action on the merit follows.

Those sections of Title 35, US code, not included in the instant action can be found in previous office actions.

Withdrawn Objections/Rejections

2. All rejections are maintained and the arguments are addressed below.

Outstanding Objections and/or Rejections

Claims Rejections - 35 U.S.C. 102

3. Claims 1-6 and 8 are rejected under 35 U.S.C. 102(e) as being anticipated by Weidenhammer et al. (U.S. Patent No. 6,379,897) (Filing Date is ***November 9, 2000***).

For ***claim 1***, Weidenhammer et al. (see entire document) disclose methods for preparing a library of mutant nucleic acids (see Weidenhammer et al., abstract; see also column 1, paragraph, 1), which anticipates claim 1. For example, Weidenhammer et al.

disclose, **[a]** "obtaining a template nucleic acid" from biological samples (e.g., see Weidenhammer et al., column 3, lines 35-54, "sequence of interest are amplified from a fixed amount of template generated from the reverse transcription of the mRNA population isolated from the biological sample"; see also column 7, lines 45-62; see also column 8, paragraphs 2-3; see also Examples). In addition, Weidenhammer et al. disclose **[b-d]** preparing a first and second oligonucleotide corresponding to a first and second desired mutation within said template nucleic acid and allowing them to hybridize to a template wherein said first oligonucleotide and said second oligonucleotide or non-complementary (e.g., see Weidenhammer et al., column 8, last paragraph wherein "chimeric oligonucleotide(s)" are used as primers for the library; see also column 10, lines 49-60, "The chimeric oligonucleotide will then be designed to generate the desired restriction endonuclease recognition site by altering the target sequence during primer extension. Such alterations may include changing, inserting or deleting nucleotides as necessary to generate type IIs restriction endonuclease recognition site into the amplified target"; see also column 11, paragraph 1, lines 5-7, "mutated oligonucleotide sequence [i.e., primer]"; see also column 9, last paragraph wherein the primers may be a mixture of random short polynucleotides e.g., random hexamer primers; see also column 9, paragraph 2; see especially claims 16, 19). Finally, Weidenhammer et al. disclose **[e]** subjecting the mixture of primers to linear cyclic amplification to produce a library of mutant template nucleic acids (e.g., see Weidenhammer et al., column 8, last paragraph, especially lines 44-46, "Following cDNA synthesis, the target(s) of interest may be linearly amplified by primer extension of a chimeric oligonucleotide(s) using DNA

polymerase. Linear amplification either by primer extension, as here, or by other means (such as in vitro transcription, used below), is necessary in order to allow quantitative comparison between different samples").

For ***claim 2, 4 and 8***, Weidenhammer et al. disclose that the primers can be completely random and thus would include discontiguous primers and also that the primers can bind to different mRNAs or different cDNAs which would also be discontiguous (e.g., see column 9, last paragraph; see also column 8, last paragraph, see also column 9, paragraph 2, "The sets of chimeric oligonucleotides that are used in target preparation will generally represent at least two distinct target species but may represent 10, 20, 40, or even up to 50 distinct target species"; see also claim 19).

In addition, Weidenhammer et al. disclose that both mutant and non-mutant oligonucleotides can be used (e.g., see Weidenhammer et al., column 10, last three paragraphs disclosing both "mutant" and "non-mutant" chimeric primers that bind to targets that either contain class IIs sequences or do not contain class IIs sequences, respectively).

For ***claim 3***, Weidenhammer et al. disclose oligonucleotides that are present in less than saturating conditions (e.g., see Weidenhammer et al., figure 5a; see also Examples).

For ***claim 5***, Weidenhammer et al. disclose that the "target" nucleic acids refer to a "gene" of interest (see column 7, line 11). A "gene" is a DNA segment that encodes (i.e., "corresponds") a protein and, as a result, claim 5 is anticipated (see column 7, lines 6-11).

For ***claim 6***, Weidenhammer et al. disclose that the target protein can be any target that is expressed in cells including IL1, TGFβ2, IL6, etc (e.g., see column 21, paragraph 1).

Response

4. Applicant's arguments directed to the above 35 U.S.C. § 102 rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

Applicants argue, "unlike the presently claimed invention, the final end product of the Weidenhamer et al. Patent methods is not a final gene sequence of interest that has been mutated, rather it is an amplicon that contains the desired (unmutated) gene sequence of interest ... Thus, taken as a whole, the Weidenhammer et al. Patent teach away from the presently claimed invention" (e.g., see 4/9/2004 Response, pages 5-7, especially page 7, paragraph 1).

This is not found persuasive for the following reasons:

The Examiner contends that Applicants arguments are not commensurate in scope with the claims. Nothing in Applicants' claims states that a "final gene sequence" must be must be mutated. Rather, Applicants claims only require that any "library of mutant nucleic acids" be produced, which would read on the mutated amplicons disclosed by Weidenhammer et al. (see rejection above). Thus, Weidenhammer et al. does NOT teach away from Applicants' claimed invention because Applicants' claimed invention is broad enough to encompass the mutated amplicons disclosed by Weidenhammer et al.

Accordingly, the 35 U.S.C. 102 rejection cited above is hereby maintained.

5. Claims 1-6 and 8 are rejected under 35 U.S.C. 102(e) as being anticipated by Caldwell et al. (U.S. Patent No. 6,582,914) (Filing Date is ***October 26, 2000***) in view of the present specification (e.g., pages 10 and 21-22) and Saluz et al. (Saluz, H.; Jost, J.-P. "A simple high-resolution procedure to study DNA methylation and in vivo DNA-protein interactions on a single-copy gene level in higher eukaryotes" PNAS 1989, 86, 2602-2606) and Kun et al. (Kuhn, P.; Knapp, M.; Soltis, S. M.; Ganshaw, G.; Thoene, M.; Bott, R. "The 0.78 A Structure of a Serine Proteinas: Bacillus lentus Subilisin" *Biochemistry* **1998**, 37, 13446-13452.) to demonstrate inherency. MPEP 2131.01(d) permits the citation of references or evidence in an anticipation rejection under 35 U.S.C. 102 in order to show that a characteristic not disclosed in the reference is inherent.

For ***claim 1***, Caldwell et al. (see entire document) disclose methods for generating a library of oligonucleotides comprising a controlled distribution of mutations (see Caldwell et al., abstract), which anticipates claim 1. For example, Caldwell et al. disclose, **[a]** "obtaining a template nucleic acid" (e.g., see Caldwell et al., claim 1, step (a)). In addition, Caldwell et al. disclose **[b-d]** preparing a first and second oligonucleotide corresponding to a first and second desired mutation within said template nucleic acid and allowing them to hybridize to a template wherein said first and second oligonucleotide are non-complementary (e.g., see Caldwell et al., claim 1, step (c); see also figures 1-2 showing "non-complementary" primers e.g., A, B, C and D; see also Summary of the Invention; see also Example in columns 25-26 and Table 2 therein

showing "non-complementary" nucleic acids used to produce library). Furthermore, Caldwell et al. disclose that the first and second oligonucleotide can be non-complementary (e.g., see Caldwell et al., figures 1-2 showing non-complementary primers; see also Summary of invention). Finally, Caldwell et al. disclose **[c]** subjecting the mixture of primers to linear cyclic amplification to produce a library of mutant template nucleic acids (e.g., see Caldwell et al., column 11, lines 25-26, "long products increases linearly because they are produce only from the original nucleic acid"; see also claim 1; see also Summary of Invention).

In addition, it should be noted that although the Example in Caldwell et al. (e.g., se columns 25-26) does not explicitly state that the 12 mutagenic oligonucleotides used to produce the subtilisin mutant library accumulate in a linear fashion (e.g., the Example states that "PCR" is being used), the Examiner contends that the mutant library members are increasing at a linear rate because only "one" mutagenic primer is used for each library member and thus linear amplification would be inherent. That is "exponential" PCR growth requires "two" primers (i.e., one primer for each parent strand) whereas "linear" PCR would be produced by just "one" primer (i.e., one for both parent strands). Thus, the Examiner contends that Caldwell's use of the word "PCR" refers broadly to "linear" PCR as well as "exponential" PCR and thus clearly anticipates the claimed invention (see also Applicants' specification, page 6, lines 21-22, wherein Applicants disclose using only one primer for each strand as a preferred embodiment for generating a linear cyclic amplification reaction, "For example, it is possible, and preferred in situations where it is desired to add more than 3 mutations, to use only one primer for

each mutation"). Consistent with this interpretation is Caldwell's disclosure of the "Taq" polymerase, which only elongates the DNA in the 5' to 3' direction and thus can only increase target DNA in a linear fashion (e.g., see Caldwell et al. column 12, line 58 and compare to Saluz et al., page 2603, column 1, first full paragraph; see also Applicants' specification, page 10, line 19 which discloses the "Taq" polymerase as a preferred enzyme for generating linear amplification reactions) (Saluz, H.; Jost, J.-P. "A simple high-resolution procedure to study DNA methylation and in vivo DNA-protein interactions on a single-copy gene level in higher eukaryotes" PNAS 1989, 86, 2602-2606). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

Finally, it should also be noted that the references in which are incorporated by reference in Caldwell explicitly refer to the use of "linear" PCR (e.g., see Gyllensten et al., column 3, line 45, wherein linear accumulation of ssDNA is disclosed) and thus would also anticipate the claimed invention because this reference was incorporated by reference into Caldwell and thus represents part of the Caldwell et al. disclosure.

For ***claim 2,*** Caldwell et al. disclose that oligonucleotides in said steps (b) and (c) are discontiguous (e.g., see Caldwell et al., lines 26-31; see also figures 1-2; see also Summary of Invention; see also column 26, Tables 2-3).

For ***claim 3***, Caldwell et al. disclose oligonucleotides that are present in less than saturating conditions (e.g., see Caldwell et al., claim 1, step (e); see also Example in specification, column 26, paragraph 1 wherein "9 nM" for "each" primer is disclosed which is less than saturation because 0.8 mM total dNTPs are used on a 269-amino acid residue *Bacillus lentus* Subtilisin i.e., 9 nM << ~ 5 μm (e.g., see specification page 7, last paragraph wherein calculation for Bacillus lentus Subtilisin would be 0.8/(2 nucleic acid strands × (269 amino acids × 3 nucleotides/amino acid)). Although the reference does not explicitly mention the length of the *Bacillus lentus* Subtilisin used (i.e., 269 amino acids) the Examiner contends that the length would be the same as that disclosed in the literature for *Bacillus lentus* Subtilisin (e.g., see Kuhn et al., abstract) and, as a result, the calculation shown above would apply.

For ***claim 4***, Caldwell et al. further disclose non-mutagenic primers (e.g., see Caldwell et al., abstract).

For ***claims 5-6***, Caldwell et al. disclose protein products selected from an enzyme, hormone, vaccine, antibody, etc. (e.g., see Caldwell et al., claim 5).

For ***claim 8***, Caldwell et al. disclose more than two said non-mutagenic primers (e.g., see Caldwell et al., abstract, see also figures 1-2, see also column 7, paragraph 2).

Response

6. Applicant's arguments directed to the above 35 U.S.C. § 102 rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified

from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue that the Caldwell et al. Patent "clearly relies upon [exponential] PCR" in contrast to the linear cyclic amplification and cite several passages in support of this position (see 4/9/2004 Response, pages 7-10, especially page 8, middle paragraph).

[2] Applicants argue that "This [i.e., the long products/megaprimer amplification] is very different from the LCR method, in which the desired end-product accumulates at a linear rate relative to the number of cycles ... In order to more clearly define the claimed invention, Applicants have deleted the word "template" in step (e) of Claim 1. Thus, it is clear that the desired end-product of the LCR method of the presently claimed invention is a library of mutant nucleic acids" (e.g., see 4/9/2004 Response, pages 7-10, especially page 9, paragraph 1).

This is not found persuasive for the following reasons:

[1] The Examiner respectfully disagrees with Applicants' assessment of Caldwell et al. For example, Caldwell et al. explicitly state that a "variety of [amplification] techniques" can be used with their invention and that any illustrations in the patent are "not intended to be limiting regarding the variety of [amplification] techniques that can be used" and specifically reference Gyllensten et al. which does disclose a linear amplification technique i.e., asymmetric PCR (e.g., see Gyllensten et al., column 3, line 45).

In addition, Caldwell et al. do provide and example wherein the mutants are "linearly" produced (e.g., see rejection above referring to subtilisin mutant library) and also disclose enzymes that ONLY produce nucleic acids in a "linear" fashion (e.g., see rejection above referring to the Taq polymerase).

Finally, Caldwell et al. provide an example wherein "long products" or "megaprimers" are being produced by linear amplification (e.g., see column 11, lines 25-26, "long products increases linearly because they are produce only from the original nucleic acid"), which do represent a library of mutant nucleic acids.

[2] The Examiner contends that Applicants arguments are not commensurate in scope with the claims. Nothing in Applicants' claims requires that the mutant nucleic acids be "end-products" as Applicants purport. Rather, Applicants claims only require that any "library of mutant nucleic acids" be produced, which would read on the long products/megaprimers disclosed by Caldwell et al. (see rejection above). Furthermore, Applicants admit in their arguments that the mutant nucleic acids do not have to be "end-products" by stating, "Of course, this library would find use in additional rounds of LCR in which new libraries are generated" (e.g., see 4/9/2004 Response, page 9, paragraph 1, last sentence), which implies that the mutant nucleic acids can be "intermediates" (i.e., not "end-products") that are subsequently used to make additional libraries (just as the long products/megaprimers disclosed by Caldwell et al. are used to make additional libraries).

Accordingly, the 35 U.S.C. 102 rejection cited above is hereby maintained.

New Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1-6 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bauer et al. (US Patent No. 5,932,419) (Date of Patent is **August 3, 1999**) and Stemmer et al. (US Patent No. 5,512,463) (Date of Patent is **April 30, 1996**) (IDS 4/4/2003 Submissions).

For ***claim 1***, Bauer et al. disclose a method for introducing site-directed mutations into circular DNA molecules of interest by means of mutagenic primer pairs (see Bauer et al., entire document, especially abstract), which reads on claim 1. For example, Bauer et al. disclose using a double stranded circular DNA template (see Bauer et al., column 2 lines 42-45; see also column 6, line 36 showing that single stranded DNA may also be used as templates), which reads on "obtaining a template nucleic acid" in claims 1(a). Furthermore, Bauer et al. disclose the use of mutagenic primer "pairs" that contain at least one mutation site with respect to the target sequence (see Bauer et al., column 2, lines 44-46; see also column 4 lines 37-47; see also column 6, last paragraph), which

reads on a "first" and "second" oligonucleotide in claim 1 (b) and (c). Bauer et al. disclose hybridizing said mutageneic primer pairs to the target sequence (see Bauer et al., column 2, lines 51-52), which reads on claim 1 (d). Furthermore, Bauer et al. disclose the production of more than one mutant strand (i.e., a library of mutant template nucleic acids) via linear cyclic amplification reactions (see Bauer et al., column 2, last paragraph; see especially line 56 and lines 61-62; see also column 7, last paragraph and column 8), which reads on claim 1 (e).

For ***claim 3***, Bauer et al. disclose first and second oligonucleotides at a concentration of 100 ng/ul (see Bauer et al., column 12, lines 47 and 49), which reads on claim 3 because 100 ng/ul is less than saturation concentration.

For ***claim 4***, Bauer et al. disclose that the transformants may contain non-mutanized parent strands that are eventually digested AFTER several cycles of linear cyclic amplification (see Bauer et al., column 9, paragraph 1).

For ***claims 5-6***, Bauer et al. disclose a template strand that corresponds to the lacZ protein product i.e., β-galactosidase enzyme (see Bauer et al., column 12, "EXAMPLES").

The prior art teaching of Bauer et al. differs from the claimed invention as follows:

For ***claims 1-2***, the prior art teaching of Bauer et al. differ from the claimed invention by not specifically reciting the use of "discontiguous" primers or "non-complementary" primers. Bauer et al. only teach the use of "overlapping" or "partially overlapping" primers (e.g., see Bauer et al., column 7, lines 10-12).

For ***claim 8***, the prior art teaching of Bauer et al. differ from the claimed invention by not specifically reciting the use of "more than two ... non-mutagenic oligonucleotides."

However, Stemmer et al. teaches the following limitations that are deficient in Bauer et al.:

For ***claims 1-2***, Stemmer et al. (see entire document) teach that mutagenic primers are both contiguous/discontiguous and complementary/non-complementary (see Stemmer et al., column 17, lines 20-33, e.g., "The primers may be ... non-overlapping"; see more generally columns 15-21 i.e., the library mutagenesis section).

For ***claim 8***, Stemmer et al. also teach the use of "non-mutagentic" primer populations i.e., more than two (e.g., see column 6, line 11).

It would have been obvious to one skilled in the art at the time the invention was made to replace the "exponential" amplification (i.e., PCR) method as taught by Stemmer et al. for making combinatorial nucleic acid libraries with the "linear" amplification as taught by Bauer et al. because Bauer et al. explicitly states that "linear" amplification is better than "exponential" amplification because it does not require a "ligation" step which would "reduce the time and expense required to carry out ... conventional methods of site directed mutagenesis" (see Bauer et al., column 11, lines 36-40). Consequently, one of ordinary skill in the art would have been motivated to use the "linear" amplification as taught by Bauer et al. "to reduce the time and expense" for generating libraries and transforming host cells as mentioned above. Furthermore, one of ordinary skill in the art would have reasonably expected to be successful because Stemmer et al. teach that both

"overlapping" and "non-overlapping" primers can be used to generate the nucleic acid libraries which would encompass the "overlapping" primers or "partially overlapping" primers disclosed by Bauer et al. (see Bauer et al., column 7, lines 10-12).

Non-Statutory Double Patenting

9. Claims 1-6 and 8 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-17 of U.S. Patent Application No. 20020160389 A1 (referred to as '389) in view of Stemmer et al. (US Patent No. 5,512,463) (Date of Patent is **April 30, 1996**).

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examiner application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1986).

Here, claims 1-17 of '389 recite the exact same method steps as those claimed by Applicants with the exception that the method of claims 1-17 in '389 fail to disclose primers that are "non-complementary" (e.g., compare claim 1 of '389 to claim 1 of the present application wherein [a] obtaining a template nucleic acid, [b-c] preparing a first and second oligonucleotide corresponding to a first and second desired mutation, [d] mixing the oligonucleotides so as to hybridize said oligonucleotides to a template, [d] subjecting the mixture to linear cyclic amplification is disclosed). The '389 patent also discloses [e] "discontiguous" primers (compare

claim 2 of '389 to claim 2 of the present application), [f] less than saturation conditions (compare claim 3 of '389 to claim 3 of the present application), [g] the use of non-mutagenic oligonucleotides (compare claim 4 of '389 to claim 4 of the present application), [h] a template that corresponds to a desired protein product including, for example, enzymes (e.g., compare claims 5-6 of '389 to 5-6 of the present application) and [i] more than two non-mutagenic primers (e.g., compare claims 4 and 9 of '389 to claim 8 of the present application). are disclosed; see also claim 3 wherein saturation concentration is disclosed; see also claims 5-6 wherein an enzyme "desired protein product is disclosed). However, Stemmer et al. teach "non-complementary oligonucleotides (see 35 U.S.C. § 103(a) rejection above, which is incorporated in its entirety herein by reference) as does claim 2 of the '389 patent which refers to "discontiguous" primers that would encompass "non-complementary" primers. It would have been obvious to modify the method of claims 1-6 and 8 of '389 with "non-complementary" primers as taught by Stemmer et al. because the teachings of Stemmer et al. falls within the scope of the claims 1-6 and 8 of '389 (i.e., the references represent analogous art) and the combined teachings Stemmer et al. explicitly state both "overlapping" and "non-overlapping" primers can be used to generate nucleic acid libraries (see Stemmer et al., column 17, lines 20-33, e.g., "The primers may be ... non-overlapping"; see more generally columns 15-21 i.e., the library mutagenesis section). In addition, the '389 patent teaches toward "non-complementary" primers in claim 2 by disclosing "discontiguous" primers.

This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is (571) 272-0811.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.
June 25, 2004

BENNETT CELSA
PRIMARY EXAMINER